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Immunology

Immunoglobulin heavy chain gene rearrangement and transcription in murine T cell hybrids and T lymphomas

(immunoglobulin gene polymorphism/polysomal mRNA)

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ABSTRACT **We have examined the arrangement of immunoglobulin heavy chain constant (C_H) and joining (J_H) region genes in murine T cell hybrid lines and in T lymphomas. C_H genes derived from both parental cell types were present in all hybrids for which polymorphism in sequences flanking C_H genes permitted us to distinguish parental C_H genes. All T lymphomas and T cell hybrids retained the C_α gene in germ-line configuration and all but one cell line had germ-line C_μ genes. Novel DNA fragments reactive with J_H probes were observed in six of nine T cell hybrids, as well as in two T lymphomas, WEHI7.1 and YAC-1, but not in the fusion parent, BW5147. No RNA homologous to $C_{\gamma 2b}$, C_α, or λ genes was detected in any of the T cell lines. T cell lines contained poly(A)$^+$ RNA homologous to a C_μ cDNA probe. More importantly, in several cell lines the C_μ RNAs were associated with membrane-bound polyribosomes. These results suggest that both J_H rearrangements and C_μ RNA production occur in at least some mature, antigen-specific T cells. They may therefore reflect events in normal T cell development and function related to those involved in the generation of the T receptor for antigen.**

Much is known about the molecular biology of immunoglobulins. Ig heavy (H) and light (L) chain genes are not inherited intact in the germ line but are generated during B cell development by somatic rearrangement and mutation of distinct germ-line variable (*V*), joining region (*J*), and diversity region (*D*) (in H chains) and constant (*C*) genes (1). These somatic events are specific in that they have not been detected in nonlymphoid cells. However, the process is error prone: some Ig gene rearrangements found in B cells are aberrant and cannot encode functional H or L chains (2). Processed RNA transcripts of aberrantly rearranged and germ-line Ig genes have been observed (3).

The T cell receptor for antigen is less well understood. It apparently bears determinants closely related to B cell H chain V regions (4). Genes encoding T cell surface antigens that are closely associated with the C region of the receptor have been mapped to chromosome 12 in the mouse, near *Igh* (5). J_H genes can undergo rearrangement in some T cell lines and T lymphomas (6–8). Moreover, the Ig C_μ gene is transcribed in normal mouse thymocytes (9) and in some murine T lymphoma cell lines (6, 10). T cell C_μ RNAs differ in size from authentic μ chain mRNAs [2.4 and 2.7 kilobases (kb)] but include all the coding sequences of the C_μ gene (11). Genetically homogeneous, antigen-specific T cell populations are needed to assess the relevance of these molecular events to T cell function. Antigen-specific T cell hybrids can be generated by fusing purified, antigen-specific primary T cells with cells of the culture-adapted murine T lymphoma line BW5147. Cloned lines derived from the initial hybrid cell population can be maintained in culture. All such lines are Ig$^-$ and many continue to express the antigen specificity and Thy-1 phenotype of the primary T cell parent (12–14).

To study Ig H chain gene structure and expression in normal murine T cells, we have applied nucleic acid blotting procedures to genomic DNAs and poly(A)$^+$ RNAs from nine antigen-specific T cell hybrids and three T lymphomas. Rearrangement of Ig J_H genes occurs in at least some classes of mature, antigen-specific T cells. Furthermore, C_μ RNA is synthesized and found on polyribosomes in some T lymphomas and T cell hybrids.

MATERIALS AND METHODS

Cell Lines. Murine T cell hybrids were prepared and characterized as described (12–14). T lymphomas WEHI7.1 and YAC-1 were obtained from N. L. Warner. T lymphoma BW5147 was obtained from R. Goldsby. All T cell lines lacked surface Ig as determined by immunofluorescence. The IgG1-producing mouse myeloma P3X63 was a gift of C. Milstein. IgM-secreting B cell hybridomas 22.1.6 (15) and CHD 2-12 were from A. Marshak-Rothstein and S. Carson, respectively. All three B cell lines are of BALB/c origin. AK2.2 is an (A/J × BALB/c) azobenzenearsonate-specific, IgG-producing B cell hybrid. B and T cell lines were grown in suspension culture in Dulbecco's modified Eagle's medium supplemented with 10% heat-inactivated newborn bovine serum (WEHI7.1, BW5147, 29P5, 63D11), with 10% heat-inactivated horse serum (AK2.2), or with 10% heat-inactivated fetal bovine serum (all other lymphoid cell lines). The LMTK$^-$ subline of mouse L cells was grown in monolayer culture in α-modified Eagle's medium plus 5% fetal bovine serum. Media and sera were from GIBCO.

Nucleic Acid Preparation and Analysis. DNA was purified and subjected to Southern blot analysis as described (16).

Total cellular RNA was prepared by a modification of the method of Auffray and Rougeon (17). Frozen cell pellets were resuspended in 3 M LiCl/6 M urea and sonicated briefly to shear DNA. RNA was precipitated overnight at 0°C, pelleted through a cushion of 50% sucrose/3 M LiCl/6 M urea by centrifugation at 17,500 × *g* for 20 min, redissolved in 0.1 M NaCl/0.01 M Tris·HCl, pH 7.5/0.1% $NaDodSO_4$, extracted with one volume of chloroform/isoamyl alcohol, 24:1 (vol/vol), and reprecipitated with ethanol. Cytoplasmic RNA and membrane-

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Abbreviations: V, variable; C, constant; H, heavy; L, light; J, joining region; D, diversity region; kb, kilobase(s); mbpr, membrane-bound polyribosome.

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bound polyribosome (mbpr) RNA were prepared as described by Perry and Kelley (18). Poly(A)$^+$ RNA was obtained by two cycles of chromatography on oligo(dT)-cellulose (Collaborative Research, type II) with 0.5 M NaCl/0.05 M Tris·HCl, pH 7.5/0.5% $NaDodSO_4$ as loading and wash buffer and with double-distilled H_2O as the eluting solvent. RNA was denatured with glyoxal or formamide in the presence of formaldehyde (19), fractionated by agarose gel electrophoresis (19), and transferred to nitrocellulose as described (20).

Six cloned probes were used for nucleic acid blot analysis. (All procedures were in accordance with the current National Institutes of Health guidelines on recombinant DNA.) $pAB\lambda_{II}$-1 is a cDNA corresponding to the entire V and C regions of the MOPC $315\lambda_{II}$ L chain inserted into the plasmid pBR322 (21). $p\gamma 2b$ (11)[7], $p\mu(3741)$[9], and $p\alpha(J558)$[13] are cDNAs corresponding, respectively, to the MPC1 myeloma $\gamma 2b$ C region, the 3741 myeloma μ C region, and the J558 myeloma α C region plus the J_2 DNA sequence and the 3′ third of the J558 V_H sequence, each in the plasmid pMB9 (22). pj_0 and pj_{11} are, respectively, the genomic 5′ *Bam*HI and 3′ *Bam*HI/*Eco*RI fragments of the J_H gene cluster inserted into pBR322 (22). The probes were labeled by nick translation with deoxycytidine [α-^{32}P]triphosphate (New England Nuclear) to a specific activity of $0.5–4.0 \times 10^8$ dpm per μg of DNA. Electrophoretically fractionated DNA and RNA were transferred to nitrocellulose filters and hybridized with the radiolabeled probes by standard methods (16, 20, 23).

RESULTS

Ig Genes in T Lymphomas and T Cell Hybrids. Previous papers have described the generation of somatic cell hybrids between normal murine T cells of known antigenic specificity and cells of the murine T lymphoma cell line BW5147 (12–14). All T cell lymphomas and T cell hybrids were Ig$^-$ as determined by immunofluorescence and immunodiffusion. Several hybrids retained the antigenic specificities of the immune parent (12–14).

To demonstrate that Ig C_H genes from both parental genomes had been retained, restriction fragments in the 5′ flanking sequences that differentiate Ig C_α and Ig C_μ genes of different mouse strains were assessed (Fig. 1). These experiments are summarized in Table 1. Data obtained with $p\alpha(J558)$[13] and *Hin*dIII-restricted DNA are shown in Fig. 2*A*. Analysis of DNA cut with three different restriction enzymes, using this probe and $p\mu(3741)$[9], showed that the C_α and C_μ genes of BW5147, YAC-1, and WEHI7.1 were present in germ-line configurations. The C_μ genes of the myeloma P3X63 were deleted, and those of the B cell hybridoma 22.1.6 were rearranged. In T cell hybrids 20B, 21C4, 29P5, 32-15, and 64C11, copies of the C_α and C_μ genes derived from the immune parents were present in their germ-line configurations. The hybrid 23A contained novel DNA fragments, consistent with C_μ gene rearrangement. Hybrid 63D11 contained a C57BL/6-derived germ-line C_α gene but no detectable C57BL/6 C_μ gene, suggesting deletion of this gene. Hybrid 49A ($BDF_1 \times$ AKR) could not be scored completely because its DBA parental C_H genes are indistinguishable from the BW5147 (AKR) C_H genes (22); however, its C57BL/6 C_H genes were not detected. Likewise in 51H7D the A/J C_μ gene could not be distinguished from the AKR C_μ gene.

J_H Genes Are Rearranged in Murine T Cell Lymphomas and T Cell Hybrid Lines. Rearrangements of J_H sequences are central to the formation of functional H chain genes in B cells (1). To determine whether such rearrangements had occurred in the J_H genes of our T cell hybrids, genomic DNA was digested, fractionated, and hybridized with the probes pj_0 and pj_{11}, which correspond to J_1/J_2 and J_3/J_4, respectively (Fig. 1). Only the germ-line J_H DNA fragments (2.3 and 0.9 kb) were found in the T lymphoma BW5147 and in three T cell hybrids (32-15, 49A, and 63D11). The T lymphomas WEHI7.1 and YAC-1 and six T cell hybrids yielded both germ-line and novel fragments, suggesting J_H gene rearrangement on at least one chromosome 12 homologue (Fig. 2 *B* and *C*, Table 1).

The sites at which rearrangement occurred within the J_H gene cluster in these T cells could be deduced from Southern blot data (Fig. 2 *B* and *C*, Table 1). The patterns of novel fragments in both lymphomas and two of the hybrids (20B and 29P5) were consistent with rearrangements involving J_3 or J_4. Four hybrids (21C4, 23A, 51H7D, and 64C11) had patterns indicating rearrangements involving J_2. No rearrangements involving J_1 were seen in any of the T cell hybrid lines.

The germ-line configuration of BW5147 J_H genes suggested that the novel bands in hybrid cell DNAs were due to rearrangement of the J_H genes of the immune T cell parent chro-

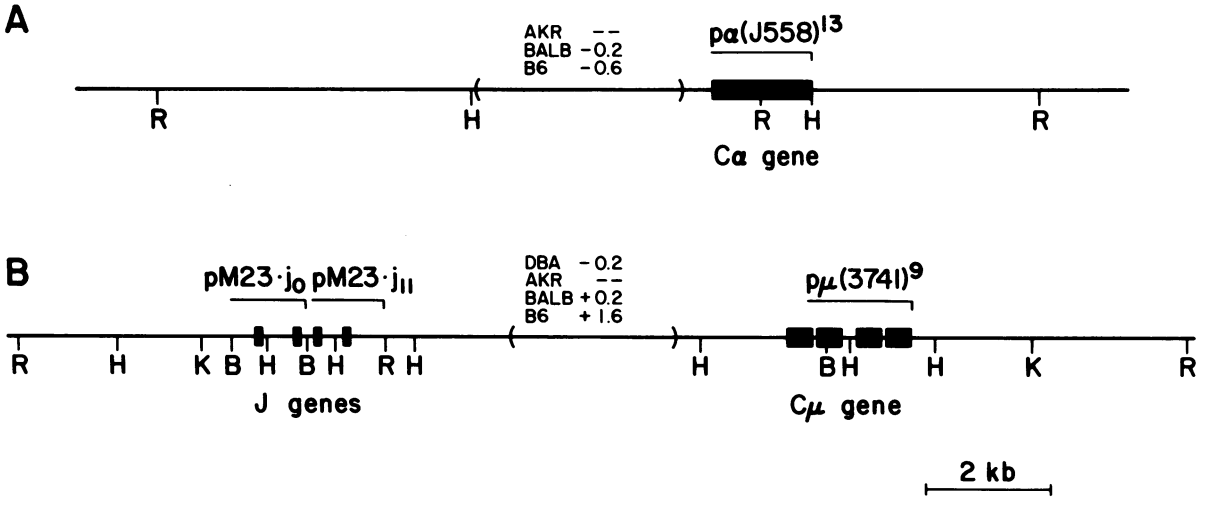

FIG. 1. Organization of Ig H chain C_α (*A*) and $J_H + C_\mu$ (*B*) genes. The relative positions and coding sequences of the genes are indicated, as are the positions of cleavage sites for the enzymes *Eco*RI (R), *Hin*dIII (H), *Bam*HI (B), and *Kpn* I (K). Only cleavage sites useful in the experiments described here are shown. The polymorphic regions adjoining the C_μ and C_α genes are in parentheses. Their sizes, as measured previously by Marcu *et al.* (24), are given relative to those of the BW5147 (AKR) cell line. Lines above the DNA map indicate the sequences contained in the probes used here (23, 24).

Table 1. Detection of C_H and J_H genes in T lymphomas and T cell hybrids

Cell line	Strain*	Presence of C_H genes from immune parent†				Presence of novel J_H fragments†					Rearrangement
		pμ(3741)[9]		pα(J558)[13]		pj_0	pj_{11}		pj_{11} + pμ(3741)[9]		
		R	B	H	R	H	H	R	B	K	
EL4.Bu	C57BL/6	14.0	10.7	5.6	9.1	2.3, 0.9	2.3, 0.9	ND	10.7	15.0	+
YAC-1	A/He	ND	ND	6.3	ND	2.3, 0.9	2.3, 0.9	9.0, 6.5	ND	12.9	J_3 or J_4
							1.8	**5.0**		**11.3**	
WEHI7.1	BALB/c	12.9	ND	6.1	ND	2.3, 0.9	2.3, 0.9	6.5	ND	14.5	J_3 or J_4
						16.8				**16.5**	
BW5147	AKR	12.5	8.7	6.3	9.7	2.3, 0.9	2.3, 0.9	6.5	8.7	13.5	+
20B	C57BL/6	+	**14.3**	+	+	+	+	**5.2**	**14.3**	**28**	J_3 or J_4
21C4	C57BL/6	+	+	+	+	**2.2**	**2.1**	**5.4**	+	ND	J_2
23A	C57BL/6	+	+	+	+	**2.9**	**3.2**	+	+	**16.3**	J_2
29P5	C57BL/6	+	**10.1**	+	+	+	**3.8**	**4.7**	**10.1**	**21**	J_3 or J_4
32-15	CBA	+	ND	+	+	+	+	+	ND	ND	+
49A	B6D2F1	CD	ND	CD	ND	+	+	+	ND	+	+
51H7D	A/J	CD	**17.3**	CD	+	**11.7**	**11.2**	**6.0**	**17.3**	+	J_2, J_3, or J_4
63D11	C57BL/6	−	ND	+	+	+	+	+	ND	ND	+
64C11	C57BL/6	+	ND	ND	+	**3.6**	**3.6**	ND	ND	ND	J_2

* Strain of origin of cell line or immune parent.

† Fragment sizes are in kb. Novel fragments (boldface) occur in addition to germ-line fragments. A + or −, germ-line fragments present or absent. CD, cannot distinguish; ND, not determined. Restriction enzymes: R, *Eco*RI; B, *Bam*HI; H, *Hin*dIII; K, *Kpn* I.

mosomes. To determine which chromosome type carried rearranged J_H genes, DNA was digested with *Bam*HI or *Kpn* I, fractionated, and hybridized with pμ(3741)[9] or pj_{11}. Each of these enzymes generates a single DNA fragment that contains the whole (*Kpn* I) or part (*Bam*HI) of the J_H gene cluster as well as the C_μ gene and its adjoining polymorphic region (Fig. 1). Each hybrid analyzed in this way contained a fragment of the size expected for the BW5147 germ-line fragment and a second fragment either of the size expected for a germ-line fragment for the normal parent or of a novel size (Fig. 3). The presence of a germ-line AKR band and a novel second band in the absence of a germ-line C57BL/6 band reactive with the pj_{11} and pμ(3741)[9] probes assigns the rearrangements at J_H in hybrids 20B and 29P5 to the C57BL/6 chromosome 12 (Table 1). An unexpected result was obtained in the case of 51H7D. *Bam*HI digests of 51H7D DNA gave a fragment of the size expected for an AKR germ-line fragment and a second fragment of novel size reactive with the pj_{11} and pμ(3741)[9] probes. Because *Hin*dIII (Fig. 2 *B* and *C*) and *Eco*RI data on this hybrid indicate a rearrangement only at J_2, we expected to see a germ-line fragment reactive with these probes (Fig. 1). The presence of the novel *Bam*HI fragment in 51H7D suggests a more complex situation involving deletions or rearrangements in the region between the J_H cluster and C_μ.

Ig Gene Transcription in T Cell Lymphomas and T Cell Hybrids. To assess Ig gene transcription in these T cell lines, total cellular poly(A)$^+$ RNA was examined by blot hybridization analysis (20) with C_H, J_H, and λ probes. No RNA species reactive with C_α, $C_{\gamma 2b}$, or λ cDNA probes was detected in any of the 12 T cell lines examined. In contrast, all 12 lines contained RNA homologous to the pμ(3741)[9] probe. The T lymphomas YAC-1 and BW5147 contained a single C_μ RNA of about 1.9 kb (Fig. 4), and WEHI7.1 contained C_μ RNAs (Fig. 4) indistinguishable in size from the 1.9-, 2.1-, 2.3-, and 3.0-kb C_μ RNAs described by Kemp *et al.* (6, 11). All T cell hybrids contained the 1.9-kb species. One hybrid, 64C11, also had a C_μ RNA that comigrated with the 2.1-kb RNA of WEHI7.1 (Fig. 4). The amount of C_μ RNA was variable among cell lines but was consistently less than that found in two μ-producing B cell hybridomas (Table 2). No RNA reactive with pμ(3741)[9] was detected in P3X63, in the IgG-producing B cell hybridoma, AK2.2, or in BALB/c mouse embryo fibroblasts.

We examined the B cell hybridomas and T cell lines for RNAs containing J_H sequences by using the probes pj_0 and pj_{11} (Fig. 1). In each of the B cell hybridomas J_H- and C_μ-reactive RNA comigrated on agarose gels, suggesting that the J_H and C_μ sequences occur on the same RNA molecules. J_H sequences were not detectable on any T cell RNAs except WEHI7.1 (unpublished data).

C_μ RNA Is Found on mbprs in T Cells. We examined the subcellular distribution of C_μ RNA in one B cell hybrid, two T lymphomas, and two T cell hybrids (Table 2) by performing blot hybridization analysis on poly(A)$^+$ RNA of nuclei, cytoplasm, and mbprs, using pμ(3741)[9] as a probe. Significant amounts of C_μ RNA were found in the mbpr fraction of two cell lines

Table 2. C_μ RNAs in T lymphomas, T cell hybrids, and B cell hybrids

Cell line	C_μ RNA, molecules/cell*	Ratio of mbpr C_μ RNA to cytoplasmic C_μ RNA†
22.1.6 (B)	740	ND
CHD2-12 (B)	757	1.0
WEHI7.1 (T)	48	0.66
BW5147 (T)	3.5	0.65
29P5 (T)	0–0.1	0.35
32-15 (T)	0.3	ND
51H7D (T)	8–17	ND
64C11 (T)	22	0.51

ND, not determined.

* Poly(A)$^+$ RNAs (0.05–1.0 μg for B cell hybrids, 1–40 μg for T cell lines) were used in blot hybridization analysis with pμ(3741)[9] as a probe. Autoradiograms were subjected to quantitative densitometry and lanes whose integrated peak intensities were proportional to poly(A)$^+$ RNA input were used to calculate C_μ RNA content per cell. The number shown is the mean of two to five measurements. The B cell hybridoma 22.1.6 was assumed to have 1% of its total poly(A)$^+$ RNA as μ mRNA (8.1×10^5 daltons). It was further assumed that 0.5% of total cellular RNA is poly(A)$^+$ and that there is 0.1 pg of poly(A)$^+$ RNA per cell.

† Cytoplasmic poly(A)$^+$ RNA fraction includes poly(A)$^+$ RNA from free polyribosomes. Contamination of mbprs by cytoplasmic RNA is assumed to be about 1% (24).

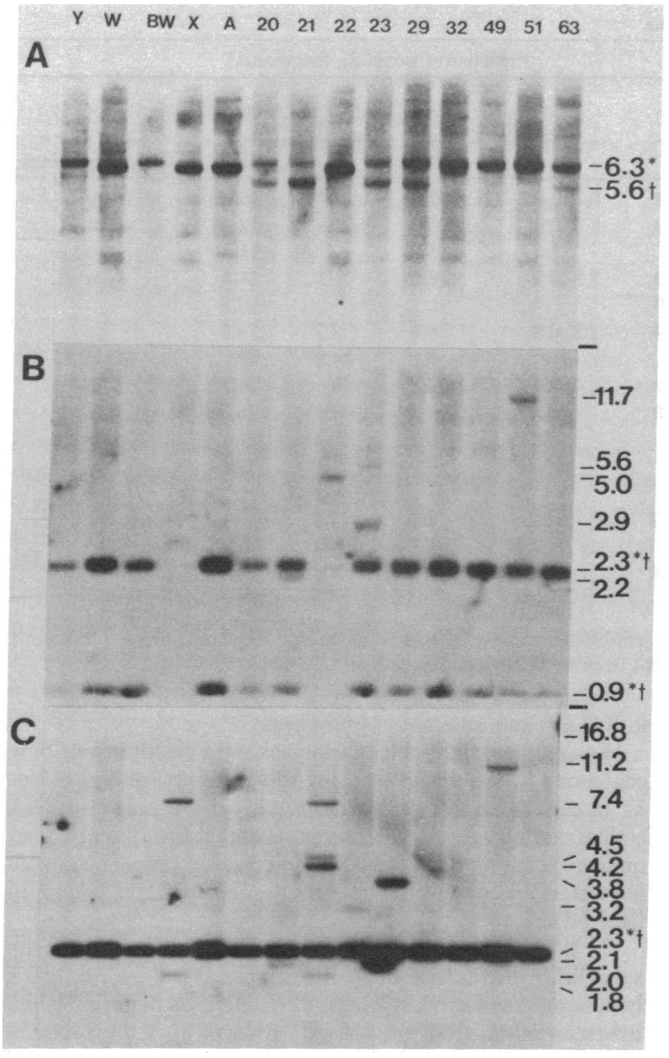

FIG. 2. Southern blots of genomic DNA from lymphoid cell lines and cell hybrids. *Hin*dIII-digested DNAs (25 μg per track) from T lymphomas YAC-1 (Y), WEHI7.1 (W), BW5147 (BW), the myeloma P3X63 (X), A9 mouse fibroblasts (A), the T cell hybrids 20B, 21C4, 23A, 29P5, 32-15, 49A, 51H7D, and 63D11 and from the B cell hybridoma 22.1.6 were fractionated on a 1% agarose slab gel, transferred to nitrocellulose, and hybridized with the probes pα(J558)[13] (*A*), pj_0 (*B*), and pj_{11} (*C*). Final washes of filters were in 45 mM NaCl/4.5 mM sodium citrate at 65°C (*A*) or in 15 mM NaCl/1.5 mM sodium citrate at 55°C (*B*, *C*). Fragment sizes in kb were calculated from their mobilities relative to *Hin*dIII-digested λ bacteriophage DNA fragments.
* Germ-line AKR gene.
† Germ-line C57BL/6 gene.

(WEHI7.1 and 64C11). In WEHI7.1 the 1.9- and 2.1-kb RNAs were the major C_μ RNA species on mbprs.

DISCUSSION

The data presented in this paper show that: murine T cell hybrids have Ig H chain genes from both parental cell types, J_H genes are rearranged in murine T cell lymphomas and T cell hybrid lines, the Ig C_μ gene is expressed in T cell lymphomas and T cell hybrids, and the C_μ RNA has poly(A) and is found on mbprs. With one exception, all of the T cell hybrids for which polymorphism in sequences flanking C_H genes permit us to distinguish parental C_H genes retain C_μ and C_α genes of both parental cell types. Because the C_μ and C_α genes are at opposite ends of the known C_H gene cluster, our results argue against models in which a T cell receptor gene is generated by splicing

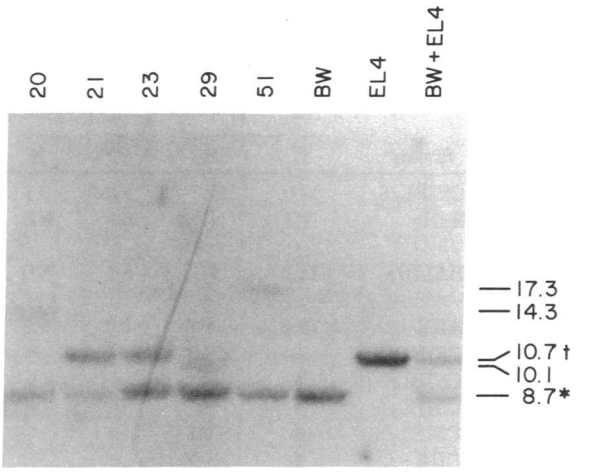

FIG. 3. J_H gene rearrangements in T cell hybrids. DNAs from T lymphomas and from T cell hybrids were digested with *Bam*HI and analyzed as described for Fig. 2 with the probe pj_{11}. The final wash of the filter was in 45 mM NaCl/4.5 mM sodium citrate at 65°C. EL4.Bu is a C57BL/6 T lymphoma that retains the germ-line configuration of these genes. The lane labeled BW+EL4 contains a 2:1 mix of BW5147 and EL4.Bu DNA.
* Germ-line AKR gene.
† Germ-line C57BL/6 gene.

a V_H gene adjacent to a "C_τ" gene at the 3′ end of the known C_H gene cluster. However, such models are not rigorously excluded by our data because we do not know how many copies of chromosome 12 occur in these T cell hybrids.

The rearrangements involving J_H in at least two T cell hybrids occur on the chromosome derived from the normal T cell parent. Because BW5147 lacks J_H rearrangements (Fig. 2 *B* and *C*), the data suggest that rearrangements occurred in the an-

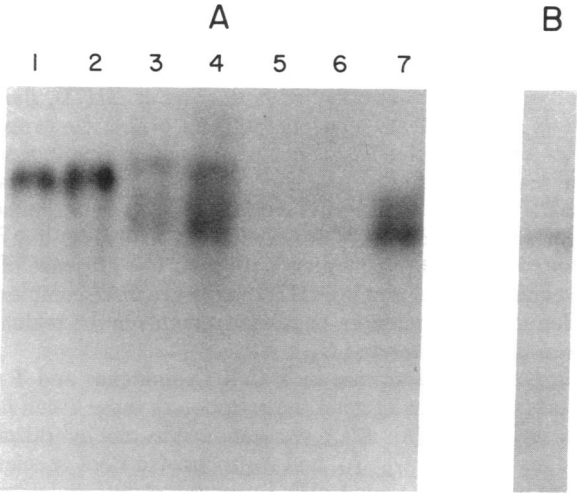

FIG. 4. Blot hybridization analysis of C_μ RNAs in T lymphomas and T cell hybrids. Total poly(A)$^+$ RNAs from B cell hybrids, T lymphomas, and T cell hybrids were denatured and fractionated by electrophoresis on a horizontal 1.6% agarose gel (21), transferred to nitrocellulose filters, and hybridized with nick-translated pμ(3741)[9] as described by Mullins *et al.* (25). Filters were washed finally in 15 mM NaCl/1.5 mM sodium citrate/0.1% $NaDodSO_4$ at 50°C and autoradiographed (*A*). *B* shows a 3-fold overexposure of lane 6 in *A*. The RNA samples in *A* are: track 1, 22.1.6, 0.4 μg; track 2, 22.1.6, 0.6 μg; track 3, WEHI7.1, 1 μg; track 4, WEHI7.1, 3 μg; track 5, unlabeled RNA markers; track 6, BW5147, 3 μg; track 7, 64C11, 3 μg. The degree to which the three lower molecular weight bands of WEHI7.1 could be resolved varied from experiment to experiment.

tigen-specific parental cells prior to fusion with BW5147. In all, 20 of 36 T cell lines described here and in previous publications (7, 8, 11, 25, 26, 29) show rearrangements involving the J_H gene complex. No obvious correlation between T cell subset and J_H rearrangement has yet emerged.

The level of C_μ RNA in BW5147 is extremely low (Table 2) and, in our hands, was detectable only under the high-sensitivity conditions provided by the formamide/formaldehyde agarose gel system. Some T cell hybrids contain more C_μ RNA than the BW5147 parent (Table 2). This might be due simply to a gene dosage effect, except in the case of 64C11, which synthesizes a C_μ RNA not found in BW5147 (Fig. 4). Further, the T cell C_μ can be recovered from mbprs, suggesting that it has a polypeptide product. Nevertheless, it has not been possible to detect polypeptides bearing the antigenic determinants of μ chains in C_μ RNA$^+$ T cell lines (27). Given the domain structure of the μ polypeptide and the preservation of antigenic determinants on isolated domains, it is unlikely that C_μ polypeptides, if synthesized, lack μ antigenic determinants. There are alternative open reading frames of 160, 170, and 200 nucleotides within the C_μ gene (28), but these include intron sequences that have been shown not to occur in T cell C_μ RNAs (11). Synthesis of very unstable polypeptides remains possible.

The J_H rearrangements and C_μ RNA transcripts in T cells reported here and elsewhere (6–11, 29, 30) may thus yield no functional product. However, the occurrence of Ig gene activity in T cells suggests that the mechanisms generating functional Ig genes in B cells act at analogous loci in T cells. Extending these analyses to more kinds of homogeneous T cell populations and to more gene probes should test the generality of Ig gene expression in T cells and the relationship of Ig gene activity to the T cell receptor for antigen.

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